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13. SUPPLEMENTARY NOTES

14. ABSTRACT

This study is a ***double blind randomized placebo-controlled clinical trial using repeated measures***. The ***objective*** is to improve recovery of functional skills for persons living in states of seriously impaired consciousness 3 to 12 months after severe TBI. This will be achieved by determining the neurobehavioral and neural effects of repetitive transcranial magnetic stimulation (rTMS), which is a non-invasive technique to stimulate the brain. The evidence of therapeutic efficacy from the literature in non-TBI related neurologic populations combined with our preliminary findings with severe TBI, indicate that rTMS merits investigation as a neurotherapeutic for severe TBI and that the proposed repetitive TMS protocol should be examined to determine effectiveness in inducing structural and functional neural plasticity and improving neurobehavioral recovery after severe TBI. ***Specific Aims***: Aim I will determine presence, direction and sustainability of rTMS-induced neurobehavioral effects measured with the Disability Rating Scale. Aim II will determine the presence, direction and sustainability of rTMS-induced changes in functional neural activation and whether or not these changes correlate with improving neurobehavioral function. Aim III will examine the effect of rTMS on white fiber tracts and whether or not the rTMS-related effects correlate with improving neurobehavioral function. Aim IV addresses the need to confirm rTMS safety for severe TBI.

15. SUBJECT TERMS

Disability Rating Scale (DRS), Neurobehavioral, Repetitive Transcranial Magnetic Stimulation (rTMS), Traumatic Brain Injury (TBI), Vegetative (VS), Minimally Conscious (MCS)

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1. **INTRODUCTION:** The rationale, based on published evidence and pilot data from three subjects, indicate that repetitive Transcranial Magnetic Stimulation (rTMS) holds promise as a treatment for severe Traumatic Brain Injury (TBI). TBI alters the lives of the patient, their family and society. Severe TBI is particularly devastating with some survivors recovering full consciousness swiftly while others remain in states of seriously impaired consciousness (SIC). Both recovery trajectories involve complex and potentially chronic cognitive and physical impairments. Evidence that cortical processing can occur even while unconscious and evidence of late recoveries continues to accumulate suggesting that SIC is a modifiable condition. Advanced medical care saves and sustains the lives of persons incurring severe TBI and there is a growing body of evidence indicating that this devastating injury is modifiable but there are few to no treatments that induce or accelerate functional and adaptive recovery for survivors of severe TBI. Optimal functional recovery after severe TBI, without targeted treatments, is unlikely. To address the need for targeted treatments that induce functional and structural changes in the brain, ultimately improving neurobehavioral functioning, we propose examining the therapeutic effectiveness of rTMS. The objective is to improve functional recovery for persons remaining in vegetative (VS) and minimally conscious (MCS) states 3 to 12 months after severe TBI. The approach is to determine the neurobehavioral effect of rTMS, the relationship between neurobehavioral changes and net neural effects, and to identify and define the neural mechanisms related to neurobehavioral improvements by providing 30 active or placebo rTMS sessions. The Disability Rating Scale (DRS) will be used at four time points to measure neurobehavioral recovery slopes. Net neural effects will be measured at three time points using fcMRI, resting state EEG (EEG-Rest), a language fMRI task and changes in EEG power spectrum when listening to a semantic processing task (EEG-Task). We will examine changes in structural integrity of fiber tracts using DTI. Measures are collected prior to, during, after and at follow up from active and placebo rTMS treatments.

2. **KEYWORDS:**

Disability Rating Scale (DRS)
Neurobehavioral
Repetitive Transcranial Magnetic Stimulation (rTMS)
Traumatic Brain Injury (TBI)
Vegetative (VS)
Minimally Conscious (MCS)

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Major Goal 1: Regulatory Requirements (Months 1-4)
Milestones: Local IRB approval and HRPO/ORP approval; **100% completed**
Major Goal 2: Coordinate Study Staff and Logistics for Study (Months 1-4)
Subtask 2a: Hiring and Training of Study Staff
Milestones: Study staff hired and trained at all 3 study sites; **100% completed**
Subtask 2b: Development of study related materials and finalize logistics

Milestones: All study materials and procedures finalized at all 3 study sites; **100% completed**

Major Goal 3: Participant Recruitment, rTMS Intervention and Follow-up (Months 4-32)
Milestones: All 58 study participants recruited and completion of research participation; **5.2% completed**

Major Goal 4: Data Analysis (Months 5-36); **0% completed**

What was accomplished under these goals?

For Major Goal 1, All 3 subject recruitment sites have full IRB and HRPO approvals necessary to recruit and enroll participants into the study.

For Major Goal 2, all study staff have been hired at all three sites.

For Major Goals 3 and 4, a civilian participant was enrolled at Northwestern and finished the TMS portion of the study on April 25th, and completed their follow-up on May 25th.This participant's surrogate learned of the trial from a physician at the Shirley Ryan Ability Lab (formerly Rehabilitation Institute of Chicago). A second civilian participant was enrolled at Northwestern, finished the TMS portion of the study on August 17th, and completed the follow-up on September 14th. This participant's surrogate learned of the trial from a physician at TIRR Memorial Hermann. During this reporting period, we have screened 35active duty/veterans and civilians of which 8were eligible and 5 are still being considered. We are currently in phase of prescreening 3 civilian participants. Additionally, we have one veteran participant who has been medically cleared for participation in the study and we are actively searching for transportation to get the participant to the Hines VA for study enrollment and 2 civilian participants have been approved for enrollment, 1 is awaiting medical clearance from a respiratory complication and 1 is in the process of being scheduled for admission to the Northwestern Memorial Hospital Clinical Research Unit.

What opportunities for training and professional development has the project provided? Nothing to report.

How were the results disseminated to communities of interest? Progress for this study was reported as an In-progress review with the Department of Defense in August.

What do you plan to do during the next reporting period to accomplish the goals?

During the next quarter, we plan to enroll and study 3 participants at the Chicago sites and 1 participant at SCVMC.

4. **IMPACT:** Nothing to report.

5. **CHANGES/PROBLEMS:**

Changes in approach are **not** anticipated at this time.

Problems: We recognize that we have deviated from the proposed patient enrollment timeline and have solutions in place to promote progress. The problems that we have experienced in the last year and the respective solutions are described below:

- During the prescreening phase, we have experienced communication barriers with external staff at long-term care facilities who have reported inconsistent information regarding the patient's medical status. While reviewing records is routine, we will now cross reference verbal reports with medical order from the preceding 24 hours.
- We are at the mercy of the provider to send acute care records which can take up to a few months to obtain.
- In order to realign our enrollment progress with what was projected, we proposed a dual enrollment at the Clinical Research Unit at Northwestern Memorial Hospital. However, we are currently limited to only one inpatient bed. We are actively working with administration at the CRU to resolve these issues and anticipate a solution to be in place for the first quarter of 2018.
- Due to recent catastrophic events, we've had difficulties in obtaining in-kind ambulance transport delaying the enrollment of qualified participants. We are currently doing extensive research on various in-kind air ambulance providers and are working diligently to secure philanthropic funding to offset the cost of transport.
- We recently received approval to distribute study recruitment material from the Landstuhl Regional Medical Center (LRMC) located near Landstuhl, Germany. LRMC is an overseas military hospital operated by the United States Army and the Department of Defense. It is the largest military hospital outside of the continental United States and serves as the nearest treatment center for wounded soldiers coming from Iraq and Afghanistan. In addition, it serves military personnel stationed in the European Union as well as their family members. This addition will broaden the pipeline for patient recruitment.

6. PRODUCTS: Nothing to Report

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

What individuals have worked on the project?

<u>Hines VA and Northwestern Memorial Hospital</u>

Name: *Theresa Pape, DrPH, MA, CCC-SLP*
Project Role: *PI*
Nearest person month worked: *1*
Contribution to Project: *Dr. Pape has overseen protocol development, staffing at each study site and overall project flow. She is part of the rotation that administers TMS treatments and acts as back up to the Research Clinical Therapist in conducting neurobehavioral testing.*

Name: *Ann Guernon, MS, CCC-SLP, CCRC*
Project Role: *Clinical Research Coordinator at Hines VA*
Nearest person month worked: *2*
Contribution to Project: *Ms. Guernon continues to oversee Hines VA, SCVMC, and Northwestern IRB amendments. Ms. Guernon has prepared and will continue to prepare all submissions to HRPO and interface with HRPO to address needed amendments. She has also been actively involved in subject recruitment and screening and data collection procedures for the enrolled participant. She is part of the rotation that administers TMS treatments and acts as back up to the Research Clinical Therapist in conducting neurobehavioral testing.*

Name: *Elyse Walsh, DPT*
Project Role: *Research Clinical Therapist*
Nearest person month worked: *2*
Contribution to Project: *Dr. Walsh is part of the rotation that provides TMS treatment and she administers neurobehavioral testing for research subject. She has also been actively involved in subject recruitment and screening and data collection procedures for the enrolled participant. She is responsible for facilitating the patient's enrollment from admission to discharge.*

Santa Clara Valley Medical Center

Name: *Ben Dirlikov*
Project Role: *Co-Investigator/EEG Technician*
Nearest person month worked: *1*
Contribution to Project: *Oversaw finance, implementation, administration, and team management at SCVMC. Preparation for EEG role as technician*

Name: *Dr. Reza Ehsanian*
Project Role: *Study Coordinator*
Nearest person month worked: *1*
Contribution to Project: *Communicated medical information to PI, provided logistical oversight among SCVMC departments Oversaw implementation, recruitment efforts, and training for neurobehavioral battery*

Name: *Jyodi Mohole*
Project Role: *Research Assistant*
Nearest person month worked: *1*
Contribution to Project: *Coordinated regulatory tasks including IRB submissions, assisted in planning recruitment and informed consent procedures. Oversaw implementation, recruitment efforts, and training for neurobehavioral battery*

Name: *Arshad Ali*
Project Role: *Research Associate*

Nearest person month worked: *1*
Contribution to Project: *Coordinated recruiting plans, planning and organizing study tasks. Oversaw implementation, recruitment efforts, and training for neurobehavioral battery*

Name: *Michael Prutton*
Project Role: *Biomedical Engineer*
Nearest person month worked: *1*
Contribution to Project: *Assisted EEG training and preparation*

Name: *Thao Duong*
Project Role: *Site PI*
Nearest person month worked: *1*
Contribution to Project: *Oversaw implementation, recruitment efforts, and training for neurobehavioral battery*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The following changes have occurred in the active other support of the PI and key personnel:

Pape, Theresa Louise-Bender

Completed

Grant No.: None (PI-Pape)
Period of Performance: 04/16-04/17
Award Amount: $10,000
Grantor: Disabled National Veterans Foundation (DVNF) Financial Assistance Grant
Grant Contact: Deborah Onaderu
Junior Program Officer
Email: donadeu@dvnf.org; Phone #202-737-0522
Objective: This funding will support the participation of Veterans and Military personnel in two funded clinical trials. The clinical trials are funded by federal research grants, but there are fiscal barriers that will prohibit severely disabled and vulnerable Veterans and Military personnel from taking advantage of an opportunity to participate in a clinical trial. One of the clinical trials enrolls patients remaining in states of seriously impaired consciousness after severe TBI and the other trial enrolls patients with mild TBI and PTSD who are experiencing persisting impairments in attention.

Grant No.: R21HD075192-01A1(PI-Pape)
Period of Performance 08/13-03/17
Time Commitment: 1.2 Calendar Months

Award Amount: $337,231
Grant Title: “Amantadine + rTMS as a Neurotherapeutic for Disorders Consciousness after TBI”
Grantor: NIH, NICHD
Grant Contact: Mary E Michel (Program Official)
Email: mm108w@nih.gov Phone: 301-496-5289 Fax: 301.402.0832
Objective: Study purpose is to examine the safety and efficacy of Amantadine combined with rTMS for persons living in Vegetative State and Minimally Conscious State at least one year after TBI. Specific aims are to (1) Demonstrate that rTMS parameters are safely tolerated when also receiving Amantadine; (2) Measure Neurobehavioral responses during the Amantadine and rTMS treatment and to distinguish these responses from those manifested with Amantadine Alone and for four independent retrospective control groups; (3) Identify brainstem thalamo-cortical connectivity that changes during provision of Amantadine + rTMS.

Conneely, Mark

Completed

Grant No.: R21HD075192-01A1(PI-Pape)
Period of Performance 08/13-03/17
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Herrold, Amy

New Support

Grant Number (PD/PI): SP0046486 (Herrold, Reilly)
Performance period: 9/2017 – 8/2018
Award Amount: $25,000
Time commitment: 0.24 Calendar Months; Co-Principal Investigator

Source of Funding: Northwestern Memorial Hospital, Women's Board, Eleanor Wood-Prince Grants Initiative
Title: Sensorimotor and cognitive effects of repetitive head trauma among female collegiate athletes.
Objective: To compare changes in brain blood flow, structure and function in mTBI and control athletes. This cross-sectional objective will assess the impact of mTBI on brain blood flow, structure and function during the subacute phase of injury. Comparing CON-C and CON-NC athletes will allow us to determine if there are differences in brain blood flow, structure and function due to subconcussive hits incurred by participating in collision sports.

Kletzel, Sandra

Completed

Grant No.: IK1RX001850 (PI-Kletzel)
Period of Performance: 06/15-06/17
Effort: .24 Calendar Months
Award Amount: $48,754
Grant Title: "Cognitive Biomarker Targets for Treatment in Veterans with Parkinson's Disease"
Grantor: VA RR&D CDA I
Grant Contact: Susan Andrese, MHA
Acting Administrative Officer, Research & Development
Grants Administrator, Research & Development (151)
Bldg. 1, Room C347
Edward Hines Jr. VA Hospital, Hines, IL 60141
Phone: 708) 202-7447 Fax: 708) 202-2684
Objective: Characterize cognitive function in a cohort of Veterans with Parkinson's Disease using neuropsychological tests and resting state functional connectivity. Identify a neural therapeutic target for Veterans with PD-MCI.

Duong, Thao

New Support

Grant #90DP0013-01-00Traumatic Brain Injury Model Systems National Database
Performance Period: January 2017 – Present
Effort Commitment: 2.5%
Role: Principal Investigator at Santa Clara Valley Medical Center
Title: The Traumatic Brain Injury National Data and Statistical Center at Craig
Funding Source: US Department of Education, National Institute on Disability and Rehabilitation Research
Grantor Contact: Dr. Cynthia Harrison-Felix
Director of Research

Craig Hospital
3425 S Clarkson St
Englewood, CO 80113
charrison-felix@craighospital.org
303.789.8565
Award Amount: Based on follow number of follow ups performed
Objective: Perform Form II follow up interviews on specified anniversaries of injury for persons enrolled in the TBI MS National Database and enter results into the Model Systems database.

Parrish, Todd

New Support

Grant No.: U01NS102038 (Corcos)
Period of Performance: 09/01/17-06/30/18
Time Commitment: 0.60 CM
Grantor: NIH/NINDS
Grant Award: $194,258
Grant title: "Neuroimaging Biomarkers in Parkinsonism: Differentiating Subtypes and Tracking Disease Progression"
Objective: This Human Connectome Project (HCP) U01 application focuses on the functional and structural connections between key brain regions in Parkinson's disease (PD), and forms of atypical Parkinsonism including the parkinsonian variant of multiple system atrophy (MSAp) and progressive supranuclear palsy (PSP). Implementing cutting-edge HCP imaging protocols in these cohorts will: 1) advance our understanding of the functional and structural connectivity between key nodes, 2) provide quantitative biomarkers that can improve early diagnosis, and 3) deliver new biological metrics for evaluating target engagement of new brain therapeutics.

What other organizations were involved as partners?

Organization Name: Northwestern University
Location of Organization: Chicago, IL, USA
Partner's Contribution to the Project: Collaboration

Organization Name: Santa Clara Valley Medical Center
Location of Organization: San Jose, CA, USA
Partner's Contribution to the Project: Collaboration

8. **SPECIAL REORTING REQUIREMENTS:** None.

9. **APPENDICES:** None

QUAD CHARTS: See attached Quad Chart.

rTMS: A Treatment to Restore Function after Severe TBI

PT130274
W81XWH-14-1-0568

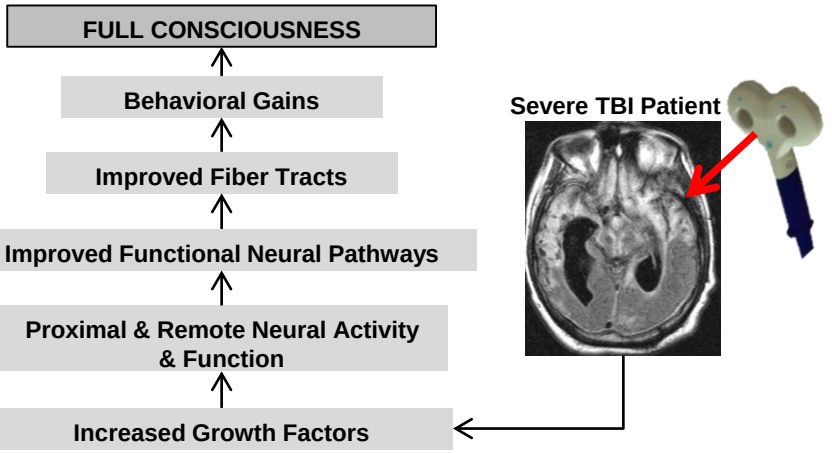
PI: Theresa Pape, DrPH **Org:** Chicago Association for Research and Education in Science (CARES) **Award Amount:** $2,993,848

Study Aims

1. Determine safety of repetitive Transcranial Magnetic Stimulation (rTMS) for severe TBI.
2. Determine if rTMS is related to improved neurobehavioral functioning during rTMS and during the 3 week follow up after stopping rTMS.
3. Determine whether rTMS associated changes in functional neural activation to auditory stimuli correspond with activation in higher order brain regions.
4. Determine whether rTMS is related to changes in white fiber tracts directly under and remote from site of stimulation.

Approach

To address the need for robust treatments that safely induce and modulate neural activity and result in improved functional recovery for severe TBI, we propose a double blind randomized sham controlled clinical trial.



rTMS changes behavior, thought to be due to rTMS up-regulation of BDNF. BDNF improves neural health and activity. As rTMS-associated neural activity increases, activation within functional neural pathways will becomes more organized.

Timeline and Cost

Activities CY	14	15	16	17	18
FDA & IRB Revisions, Contracts					
Subject Enrollment & Data Collection					
Data Entry, Processing & Analyses					
Estimated Budget ($3,000,000)					

Updated: July 2017

Goals/Milestones

CY14 & CY15 Goals – Study Start-Up
☑ Obtain local IRB and HRPO approval
☑ Obtain FDA IDE approval
CY16 Goals – Enrollment of 6 subjects
☐ Enroll 2 subjects at SCVMC & 4 at NU/Hines VA
☐ Database Entry for all 6 subjects
CY17 Goals – Enrollment of 30 subjects
☐ Enroll 15 subjects at SCVMC & 15 at NU/Hines VA
☐ Database Entry for all 30 subjects
CY18 Goals – Enrollment of 22 subjects
☐ Enroll 12 subjects at SCVMC & 10 at NU/Hines VA
☐ Complete Database Entry and Analyses
Comments/Challenges/Issues/Concerns:
Budget Expenditure to Date
Quarter Expenditure: $367,227
Grant-to-date Expenditure: $1,495,004